FEATURE

ADVANCES IN RESEARCH ON FETAL ALCOHOL SPECTRUM DISORDERS

Fetal alcohol spectrum disorders (FASD) are the broad range of neurodevelopmental and physical effects that result from prenatal exposure to alcohol. People with FASD may have facial abnormalities and growth impairments, but the most profound effects are cognitive and behavioral deficits. These deficits can contribute to lifelong learning disabilities, poor social skills, and other problems that impact daily functioning (e.g., living independently or holding a job), as well as overall health and well-being. A significant public health problem, FASD affect an estimated 1 to 5 percent of first-grade children in the United States, according to a 2018 NIAAA-supported study conducted by the Collaboration on Fetal Alcohol Spectrum Disorders Prevalence (CoFASP) and published in the *Journal of the American Medical Association*.

"Research on FASD is a priority for NIAAA, and for many years we've supported studies to understand how alcohol disrupts prenatal development and how FASD can be prevented, diagnosed, and treated," says NIAAA Director George F. Koob, Ph.D. "Basic, translational, and clinical research are providing valuable insight into the mechanisms that underlie the learning deficits and health problems associated with FASD, thereby shedding light on potential intervention strategies."

For example, in a recent study led by Wolfram Goessling, M.D., Ph.D., and Olivia Weeks at Harvard Medical School, researchers reported a connection between prenatal alcohol exposure and metabolic disorders in adults. Their analyses of a patient database at a large academic health system found that adults with FASD had an increased incidence of type 2 diabetes, lower HDL ("good") cholesterol levels, and elevated triglyceride levels compared to those without FASD. Low HDL cholesterol and elevated triglyceride levels are associated with increased risks of stroke and heart attack.

The researchers also investigated the relationships between metabolic dysfunction and prenatal alcohol exposure using a zebrafish model of FASD. When they examined alcohol-exposed zebrafish at adulthood, they found that a high-fat, high-cholesterol diet resulted in obesity and high glucose levels in male but not female zebrafish. High blood glucose is an indicator of diabetes in humans. The

IN THIS ISSUE
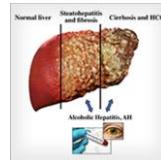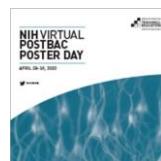
researchers also found an association between increased abdominal fat and abnormal liver development in the adult alcohol-exposed zebrafish, suggesting that the molecular mechanism for such alcohol-related pathology is a highly conserved in zebrafish and an evolutionarily basic component of physiology.

Given that alcohol is frequently used with other substances, NIAAA-supported scientists are investigating the combined effects of prenatal exposure to alcohol and substances such as tobacco. As part of the multisite Prenatal Alcohol in SIDS and Stillbirth (PASS) Network, investigators from the United States and South Africa recently reported that children born to mothers who both drank and smoked beyond the first trimester of pregnancy have a twelvefold increased risk for sudden infant death syndrome (SIDS)—the sudden, unexplained death of an infant younger than 1 year—compared to those who were unexposed or only exposed in the first trimester of pregnancy. Dual exposure to alcohol and tobacco was associated with substantially higher risk than exposure to either substance alone, suggesting that combined exposures to alcohol and tobacco have a synergistic effect on SIDS risk.

In another recent NIAAA-supported study, Kazue Hashimoto-Torii, Ph.D., of the Children's National Research Institute in Washington, D.C., and colleagues investigated the molecular mechanisms that contribute to the motor deficits associated with prenatal alcohol exposure. Previously, the researchers showed that prenatal alcohol exposure was associated with differences in expression of nearly 100 genes. More recently, they focused on the increased expression of a gene, known as *Kcnn2*, which encodes a protein involved in regulating neuron activity in brain systems associated with learning (see sidebar

> *Kccn2* stands for potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2, and is a gene that encodes a protein channel involved in regulating neuronal excitability in brain systems associated with learning.

for more information) in the motor area of the cerebral cortex in a mouse model of FASD. The researchers demonstrated that increased *Kcnn2* expression correlated with deficits in motor skill learning caused by prenatal alcohol exposure. They also observed improvements in these learning deficits when a drug was administered to inhibit activity of *Kcnn2*, suggesting that *Kcnn2* inhibitors may be a potential pharmacological intervention for certain learning disabilities in FASD.

NIAAA-supported clinical research is also focused on developing interventions to mitigate the adverse effects of prenatal alcohol exposure. Researchers at the University of Minnesota and colleagues have been investigating whether supplementing the diet with choline during early childhood brain development could improve memory and executive function in children with FASD. Choline is an essential

> Myelination is the formation of an insulating layer or sheath around neurons that allows electrical impulses to transmit quickly and efficiently.

nutrient with a key role in myelination (see sidebar) and is known to impact brain development and cognition. In a previous study led by Jeffrey Wozniak, Ph.D., the researchers showed that choline supplementation is feasible and tolerable with minimal side effects among 2- to 5-year-old children who were prenatally exposed to alcohol. In their recently published, 4-year follow-up study on the choline recipients, researchers report that children who received choline had better nonverbal intelligence, visual-spatial skills, and working and verbal memory, as well as fewer symptoms of negative behavior compared to the children who did not receive choline. It is important to note that these effects were evident years after choline administration had ended, suggesting that developmental trajectories had been altered.

"Prenatal alcohol exposure contributes to an array of lifelong physical, cognitive, and behavioral problems," says Dr. Koob. "These detrimental effects highlight the need for strategies to improve FASD prevention, screening, diagnosis, and treatment. NIAAA's recent efforts towards the development of a consensus FASD overarching research classification system could accelerate progress in these areas."

For more information, see "Consensus Meeting on Fetal Alcohol Spectrum Disorders Research Classification" and "Collaborative Initiative on Fetal Alcohol Spectrum Disorders" in this issue of the *NIAAA Spectrum*.

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Consensus Meeting on Fetal Alcohol Spectrum Disorders Research Classification

In October 2019, NIAAA held a meeting of international experts to identify essential elements for developing a single research classification system for fetal alcohol spectrum disorders (FASD). Currently, researchers around the world use a variety of classification systems to categorize individuals who are affected by prenatal alcohol exposure. The populations studied by researchers also vary greatly (e.g., clinical vs. research populations). This combination can make comparing research findings difficult and lead to uncertainty in the scientific literature.

The meeting was organized around three features of FASD: neurobehavioral impairment, dysmorphology (changes in physical features), and alcohol exposure. Deliberations of the expert panel helped to sharpen areas of consensus and narrow areas of discrepancy across current research classification systems. The panel also discussed possible framework options for a single, overarching research classification system for FASD. A consensus emerged that any such framework should fully capture the dimensionality of each of the contributing elements—physical, dysmorphology, neurobehavior, and prenatal alcohol exposure—and be adaptable across the lifespan.

Moving forward, meeting participants will test classification elements, thresholds, and frameworks in their own research databases. This process is currently underway, and the results will help experts reach consensus on a single, overarching research classification system whose adoption will harmonize international research efforts. The group plans to inform the research community of their efforts through presentations at upcoming scientific meetings.

Collaborative Initiative on Fetal Alcohol Spectrum Disorders

The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), established in 2003, is a research consortium that focuses on improving the diagnosis, prevention, and treatment of fetal alcohol spectrum disorders (FASD). It is composed of a team of multidisciplinary basic, translational, and clinical researchers from across the United States and throughout the world and addresses issues related to prenatal alcohol exposure that occur across the lifespan. Current CIFASD projects focus on brain and physical development, risk and resiliency factors, screening tools and approaches (including telemedicine), biomarker discovery, health effects in youth and adults, and a mobile health intervention. The researchers use novel techniques and approaches to move the field of FASD research forward.

For example, Christie Petrenko, Ph.D., at the University of Rochester's Mt. Hope Family Center, and Cristiano Tapparello, Ph.D., in the University's Department of Electrical and Computer Engineering, teamed up to create a mobile phone app for caregivers of children with FASD. The smartphone app, *FMF Connect*, is designed to give caregivers access to evidence-based content that can help them learn new skills to manage their children's behavior. It also helps them connect with other caregivers for support and to share ideas. The researchers recently conducted focus group testing with caregivers of children with FASD and reported the findings in the April 2020 issue of *JMIR mHealth and uHealth*. The participants related how the global themes could address some issues they face, such as limited access to services and feeling isolated. They also offered constructive feedback related to barriers to use and privacy concerns. The researchers are refining the app based on this feedback. After more testing, they plan to evaluate the efficacy of the app in a large-scale randomized controlled trial.

For more information about CIFASD, please visit https://cifasd.org.

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Petrenko, C.L.; Parr, J.; Kautz, C.; Tapparello, C; and Olson, H.C. A mobile health intervention for fetal alcohol spectrum disorders (Families Moving Forward Connect): Development and qualitative evaluation of design and functionalities. *JMIR mHealth and uHealth* 8(4):e14721, 2020. PMID: 32250274

NEWS FROM THE FIELD

PRENATAL ALCOHOL EXPOSURE CHANGES MOUSE BRAIN CIRCUITRY INVOLVED IN DECISION MAKING
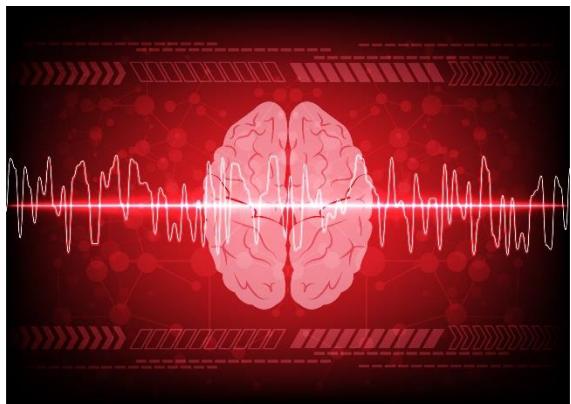
Prenatal alcohol exposure is a leading preventable cause of birth defects and neurodevelopmental abnormalities in the United States. It can lead to learning, memory, and impulsivity problems in both children and adults. In a new study conducted with mice, NIAAA scientists report that specific changes in a brain circuit involved in learning and decision making could underlie some of the behavioral effects of prenatal alcohol exposure. These findings by researchers in NIAAA's Division of Intramural Clinical and Biological Research were published online in *Nature Communications*.

In the study, the researchers exposed pregnant mice to alcohol and later tested the offspring's cognitive function using two decision-making tasks—one focusing on goal-directed decisions (actions aimed at an outcome or consequence) and the other to probe decisions based on habits (actions resulting from frequent repetition without focus on a consequence). They found that offspring that had been prenatally exposed to alcohol had different decision-making strategies compared to those without prenatal exposure— prenatally exposed mice were more likely to rely on the cognitively demanding, goal-directed decision making at the expense of the less-demanding, habit-based decision making.

The researchers went on to measure electrical activity in the dorsal striatum—a brain region involved in learning and habit formation—as the offspring engaged in the decision-making tasks. They found that changes in two neurotransmitter systems—gamma-aminobutyric acid (GABA) and endocannabinoids—were associated with the observed differences in decision making in prenatally exposed animals. Specifically, the effects of endocannabinoids on neuron activity in the dorsal striatum increased while the levels of GABA decreased. GABA is the main inhibitory neurotransmitter in the brain. Endocannabinoids are chemicals produced within the brain that modulate the overactivity of neurons such as GABA and are involved in circuitry regulation associated with many brain functions. These findings suggest that treatments targeting the GABA and endocannabinoid systems might be useful in ameliorating impaired decision making associated with prenatal alcohol exposure.

Future research could help translate this work to humans, clarifying how much these changes in behavior and circuits translate to people with a history of prenatal alcohol exposure.

Reference:

Cuzon Carlson, V.C.; Gremel, C.M.; and Lovinger, D.M. Gestational alcohol exposure disrupts cognitive function and striatal circuits in adult offspring. *Nature Communications* 11:2555, 2020. PMID: 32444624

NOTEWORTHY

Pictured are two youths who are members of the Yup'ik community in Alaska, which is collaborating with an NIAAA grantee on an alcohol-use prevention program. *Photo by Georgianna Ningeulook, Scammon Bay, Alaska.*

NIAAA TO HOST WEBINAR ON INTERVENTIONS IN AMERICAN INDIAN AND ALASKA NATIVE COMMUNITIES

Developing culturally appropriate interventions to prevent alcohol-related problems among American Indian and Alaska Native communities is a priority of NIAAA-supported research. In the Yup'ik community in Alaska, NIAAA-supported researchers and Yup'ik community leaders are collaborating to create and assess culturally compatible preventive interventions for alcohol use disorder and suicide in 12- to 18-year-olds.

On October 8 at 1 p.m., NIAAA will host a webinar using this project as a case study for creating similarly tailored interventions for American Indian and Alaska Native communities across the United States. The project utilizes history and culture as organizing principles for substance use prevention efforts with youth in indigenous communities. Join the Substance Abuse Prevention for Youth in Indigenous Communities webinar at https://www.niaaa.nih.gov/news-events/meetings-events-exhibits/webinar-substance-abuse-prevention-youth-indigenous-communities.

SPOTLIGHT

ALCOHOLIC HEPATITIS NETWORK

Normal liver Steatohepatitis and fibrosis Cirrhosis and HCC

Alcoholic Hepatitis, AH

Clinical syndrome of sudden onset of jaundice and hepatic failure
Adapted from a figure by S. Radaeva, Ph.D.
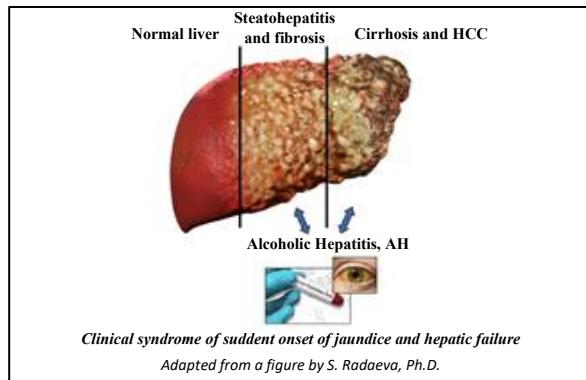
Alcoholic hepatitis (AH) is a severe, sudden-onset form of alcohol-associated liver disease (ALD) with high mortality—from 30 percent to 50 percent within 3 months of diagnosis. To stimulate translational and clinical research into the causes of and cures for AH, NIAAA funded four AH research consortia in 2012. From 2012 to 2017, the AH research consortia collaborated to draft standard definitions for the condition and to develop common data elements for clinical trials.

To optimize these efforts, in 2018 NIAAA Director George F. Koob, Ph.D., consolidated the four AH research consortia into a single network. In September of that year, the NIAAA Alcoholic Hepatitis Clinical and Translational Network was formed by funding eight sites to conduct a common Phase II clinical trial, along with studies aimed at increasing our understanding of AH pathogenesis and developing new treatment and management approaches.

Today the network is a collaborative effort of 11 clinical and translational research centers and is known as the Alcoholic Hepatitis Network, or AlcHepNet. The goal of the AlcHepNet is to collect and store clinical data to facilitate investigations of the epidemiology, diagnosis, pathophysiology, natural history, and treatment of alcoholic hepatitis, and to develop a biospecimen bank comprising plasma, DNA, and other biological specimens obtained from individuals with and without alcoholic hepatitis. Combined, these approaches will improve treatment and care for patients with this devastating liver condition.

"Better treatment and clinical care for AH is certainly on the horizon thanks to the AlcHepNet," notes Dr. Koob, "and treatment for alcohol use disorder could well become recognized as the most important determinant of long-term survival for individuals with AH. I'm also hopeful that the AlcHepNet's unparalleled scientific talent and world-class resources may uncover new biomarkers that could help shift our focus from AH treatment to prevention."

AlcHepNet Data Coordinating Centers

Indiana University–Purdue University at Indianapolis

University of Massachusetts Medical School–Worcester

AlcHepNet Research Sites (Clinical and/or Translational)

Beth Israel Deaconess Medical Center (C/T)

Cleveland Clinic Lerner College of Medicine of Case Western Reserve University (C/T)

Indiana University–Purdue University at Indianapolis (C/T)

Mayo Clinic–Rochester (C/T)

University of California, San Diego (T)

University of Louisville (C/T)

University of Pittsburgh at Pittsburgh (C/T)

University of Texas Southwestern Medical Center (C)

Virginia Commonwealth University (C/T)

Yale University (T)

SPOTLIGHT
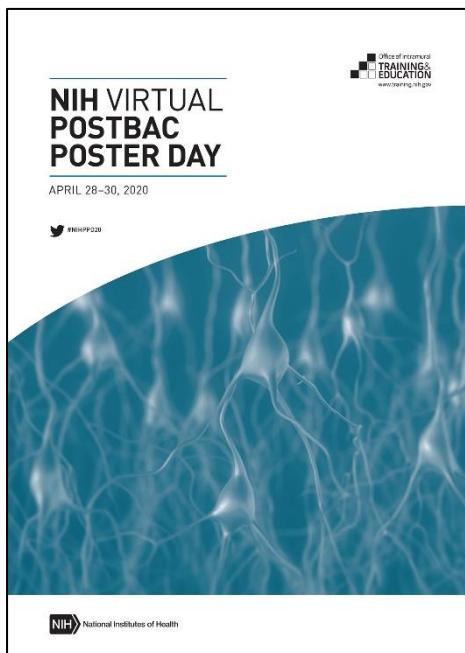
NIAAA TRAINEES NETWORK VIRTUALLY AT NATIONAL INSTITUTES OF HEALTH (NIH) POSTBAC POSTER DAY

The NIH postbac intramural research training award (IRTA) program provides recent college graduates who are planning to apply to graduate or professional school an opportunity to spend a year or two performing full-time research at NIH. NIAAA postbacs are hosted in a variety of NIAAA intramural labs located in Bethesda and Rockville, Maryland.

In late April, NIH postbaccalaureate researchers (also known as postbacs), including 33 from NIAAA laboratories, gathered online for the annual NIH Postbac Poster Day. Although this event generally takes place in person, the COVID-19 outbreak led organizers to rethink the event, making it 100 percent virtual.

Nine NIAAA postbacs received an Outstanding Poster Award at the event. Only the top 20 percent of posters received the award, based on review by teams of NIH graduate students, postdoctoral fellows, clinical fellows, staff scientists, and staff clinicians. The NIAAA postbacs who earned this award were Jacob Ballway, Kendall Coden, Danielle Kroll, Katie Teresi, Emily Vogt, Chase Weinholtz, Charles Zawatsky, Kaeli Zoretich, and Leo Zsembik.

This event proved that physical distancing does not mean social isolation. Although research had been largely put on hold at the NIH campus due to precautions for COVID-19, it did not stop these up-and-coming scientists from networking with researchers across NIH. While some postbacs were able to share data they had collected, others shared thoughtful reviews of existing literature or proposals for future projects.

SPOTLIGHT
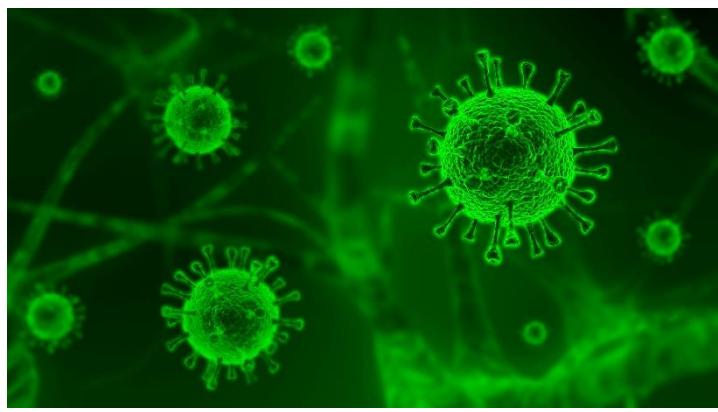
SUPPORTING RESEARCH ON ALCOHOL AND COVID-19

In response to the urgent need for research on how the ongoing COVID-19 pandemic is affecting many aspects of health, NIAAA has issued a funding opportunity to encourage research on the complex relationships between alcohol consumption and COVID-19. In addition to research on behavioral, social, and economic consequences of the pandemic, the Institute is interested in both the study of alcohol as a biological contributor to COVID-19 outcomes and in assessing the impact of the pandemic on alcohol misuse, alcohol use disorder (AUD), and the treatment of AUD. Such studies could provide not only key information on the effects of common biological pathology but also the effects of physical isolation/social isolation of alcohol misuse, AUD, and the treatment of AUD. Such information may also inform the response to future public health emergencies and provide opportunities for interventions in populations with limited access to health care.

NIAAA is also participating in funding opportunities led by other NIH Institutes to support COVID-19 research, and as a result NIAAA is encouraging the integration of alcohol-related research questions into broader areas of study. These areas include stress and mental health, nervous system effects, aging populations, maternal mortality, and health disparities. All funding opportunities related to COVID-19 are listed on the NIAAA website.

Facilitating research on the "downstream" public health effects of the COVID-19 pandemic is important for NIAAA. For example, the Institute added a COVID-19 update to the Alcohol Policy Information System (APIS). This alcohol policy information can be used by researchers to compare the effects of the COVID-19 crisis on a range of health-related outcomes across states. NIAAA also updated its surveillance report series to include monthly per capita alcohol sales data, where available. These reports will be updated as data from additional states and for subsequent months become available. This information can enable research on the impact of the COVID-19 pandemic on the nation's alcohol consumption during the ongoing evolution of the pandemic.

5 QUESTIONS WITH. . .

BILL DUNTY, PH.D.

NIAAA FASD Research Coordinator and Program Director, Division of Metabolism and Health Effects (DMHE)

1 *How would you describe your portfolio of projects in DMHE?*

My grant portfolio includes research on the health consequences of prenatal alcohol exposure. These studies include basic research on the harmful effects of prenatal alcohol exposure as well as clinical studies of individuals with fetal alcohol spectrum disorders, or FASD. FASD is an umbrella term for a range of physical, cognitive, and behavioral disorders caused by prenatal alcohol exposure that appear at any time during childhood and last a lifetime.

I also serve as the Project Scientist for the NIAAA-supported Collaborative Initiative on Fetal Alcohol Spectrum Disorders, or CIFASD, a multidisciplinary consortium of projects to enhance diagnoses of FASD at different stages of the lifespan based on biological, physical, and behavioral assessments and to improve outcomes in individuals with FASD. Prior to becoming NIAAA's FASD Research Coordinator in 2018, I also managed grants related to alcohol biosensors and alcohol-associated carcinogenesis.

2 *You're a member of the Executive Committee of the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD). What is NIAAA's role in ICCFASD?*

ICCFASD fosters improved communication and collaboration among disciplines and federal agencies that address a wide range of issues related to prenatal alcohol exposure. In 1996, following recommendations from the Institute of Medicine, Congress charged NIAAA with chairing ICCFASD, which currently comprises agencies across the federal government. This collaboration across agencies is important because the responsibility for addressing the many issues relevant to FASD transcends the mission and resources of any single agency or program. ICCFASD also interacts with researchers, clinicians, professional associations, advocacy organizations, and the general public, with the goals of increasing awareness of FASD, improving education for professionals and others who interact with individuals affected by FASD, and promoting the implementation of evidence-based approaches to address the needs of children and adults who live with FASD and their families.

Today, NIAAA continues to sponsor ICCFASD and our Deputy Director, Dr. Patricia Powell, serves as the ICCFASD Chair. As part of the committee, our Institute generates and disseminates basic, translational, and clinical research findings on FASD. My role as NIAAA's FASD Research Coordinator is to provide updates on NIAAA activities in this area, exchange information, and advance high-priority efforts identified by the committee.

3 *What are some noteworthy recent advances in FASD research?*

Identifying individuals with FASD remains a challenge, given that most children with prenatal alcohol exposure do not meet the diagnostic criteria for full-blown fetal alcohol syndrome (FAS) but nevertheless possess significant neurobehavioral deficits and associated secondary disabilities. Over the past few years, NIAAA-funded investigators have taken great strides to improve the capabilities in clinical recognition of FASD. Research in this area includes improving FAS/FASD facial recognition through 3-dimensional (3D) photography and computer analyses among individuals across different age groups and racial/ethnic backgrounds, and refining neurobehavioral-based screening tools for pediatricians and psychologists to better identify children exposed to alcohol prenatally.

Another key challenge facing clinicians is the ability to recognize alcohol consumption during pregnancy and identify prenatal alcohol exposure among newborns. To address this need, NIAAA-supported researchers are exploring the use of novel methodologies such as 3D fetal ultrasound, blood-based biomarkers, and physiological measures to improve earlier identification. Although FASD lasts a lifetime, earlier identification of infants and very young children affected by prenatal alcohol exposure may increase the effectiveness of intervention strategies to improve a child's development.

4 *What are some of the most promising areas for clinical breakthroughs in FASD research on the horizon?*

Two promising areas come to mind. The first area focuses on the development of interventions to help individuals affected by prenatal alcohol exposure. Over the last 10 years, our largest investment in this area has supported basic and clinical research exploring the efficacy of choline supplementation as a nutritional intervention for FASD. Positive benefits have been reported on growth and memory performance among infants born to women who receive choline during pregnancy. Most recently, researchers report that giving supplements of choline to 2- to-5-year-old children who were exposed to alcohol before birth improves aspects of cognition and behavior assessed at 4 years post-treatment.

A second area is emerging research on how prenatal alcohol exposure may also increase the risk for chronic diseases and health conditions later in adulthood. This area of research barely existed in the alcohol field 7 to 8 years ago. NIAAA-funded investigators in our CIFASD consortium are currently conducting a health survey of adults with known alcohol exposure or an FASD diagnosis to help establish the natural history of these disorders in this vulnerable population. The ability of alcohol to reprogram fetal physiology and enhance disease risk later in life represents an underappreciated public health concern. Future findings in this area may be critical in optimizing strategies for disease prevention among individuals across the spectrum of FASD.

5 *Outside of work, people say you're an accomplished photographer. In fact, some of your photography has adorned the walls of the NIAAA workplace. How did that get started?*

Although I've had a professional-grade camera for many years, it wasn't until 2015, when I took a series of introductory digital photography courses, that I learned how to use it and began to appreciate the principles of photography. Since then, my interests have shifted from taking pictures of my kids playing sports to landscapes and wildlife photography, and now to candid shots. Currently, I volunteer as a photographer for the Indy Honor Flight, a nonprofit organization that transports military veterans to visit their national memorials in Washington, D.C. In capturing moments of emotion, I can convey a sense of their service and sacrifice to their family members back home in Indiana who cannot travel with them.